Regulatory Update

Craig Kiester, RPh
Senior Regulatory Review Officer
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Overview

- Excipients
- Control Correspondences
- PET products

Justification

- Products required to be Q1/Q2 may be within ±5% of an approved ingredient, but cannot exceed the highest amount within our databases
- Each inactive ingredient must be justified unless it is ≤0.1% of the total drug product weight
- Dosage Unit vs MDD justification

Excipients that exceed approved limits

- Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, May 2005
- Process
  - If you can not justify an excipient at the level you are proposing in the IID, please submit Pharm/Tox data as instructed in the guidance
  - This data will be consulted to OND to ensure that the excipient does not have an effect on safety and/or efficacy of the product

Solid Oral Dosage Forms

- Must be justified via the same route of administration as proposed product
  - i.e. Buccal, Sublingual, Oral
- Route may be influenced by absorption site
  - Orally Disintegrating Tablet
  - Some Buccal products
- “Generic” descriptions do not always justify an inactive
  - Inactive may be a different grade or different product

Oral Solutions

- Not required to be Quantitatively (Q1) or Qualitatively (Q2) the same as the RLD
  - However, be aware that differing sugar alcohols (eg. Sorbitol) can cause a problem with bioavailability

- Eligible for Bio Waiver under 21 CFR 320.22(b)(3)

Ophthalmics

- **Required** to be Q1 and Q2 with the RLD

- 21 CFR 314.94(a)(9)(iv): applicants may still formulate in accordance with this regulation, but waivers of in-vivo BE will not be entertained.

  - Determination that changes in the formulation may adversely affect the efficacy of the drug product

Ophthalmics cont.

- If you decide to make any change to the preservative, buffer, tonicity adjuster, thickening agent
- BE study must submitted at time of filing
- If no BE study is submitted we will Refuse to Receive your application
- 505(b)(2) option

Topical Products

- Includes lotions, ointments, creams, solutions, foams, gels
- Generally, solutions do not need to be Q1/Q2 with the RLD under 21 CFR 320.22(b)(3)
  - Some products that fall under the Bioequivalence Waiver will still need to provide Bioequivalence and/or Clinical studies

Topical Products cont.

- Creams and Ointments do not need to be Q1/Q2 with the RLD
  - Not eligible for Bio Waiver
  - Will need to provide Clinical studies regardless

Topical Products cont

- Must demonstrate product is a solution when administered for some products to receive a Bio Waiver
  - Example: Foam

- Changes in amounts of inactive ingredients from the RLD may require additional studies, pharm/tox data, and possibly skin irritation/sensitization studies.

Nasal Sprays

- Must be Q1/Q2 with the RLD
  - Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products, published July 2002
- Still need to provide *in-vitro* studies
  - Plume geometry, droplet size, dispersion, etc.
- If the product is a suspension, will need to provide additional *in-vivo* studies

Metered Dose Inhaler (MDI) Nebulizer Solution

- MDI's are strongly recommended to be Q1/Q2 with the RLD
- 21 CFR 314.94(a)(9)(v) allows for changes but must demonstrate changes do not affect safety or efficacy
- Products for nebulization are **not** required to be Q1/Q2 under 21 CFR 320.22(b)
- MDI's are not eligible for a waiver

Parenteral

- Q1/Q2 to the RLD is always preferred
- If an RLD is packaged with a specific diluent, the ANDA needs to also contain that diluent and be Q1/Q2 to it as well.
- May make changes in the formulation under 21 CFR 314.94(a)(9)(iii)
  - Buffer, Preservative, Antioxidant
- pH adjusters **are not** considered exception excipients
  - If the RLD has pH adjusters in the labeling, they **must be** included in the generic formulation and production batch records even if they are not utilized

Percent Amount

- Issues may occur when using percentage to justify an inactive ingredient
  - Especially prevalent with Oral solutions, Parenterals and Topical Products

- Example: The IID states an inactive ingredient is used at an amount of 90%
  - Unable to determine from this if the ingredient is presented as weight/volume (w/v), weight/weight (w/w) or volume/volume (v/v) or if this is amount per container or per dose

  - **Always provide amounts in mg/mL whenever possible**

Iron

- If an inactive ingredient contains an iron (ferric) component, the daily elemental iron intake must be taken into account
  - Occurs most often with coloring agents
- May not exceed 5 mg/day of elemental iron
  - 21 CFR 73.1200(c)
- Provide justification within the components and composition section (3.2.P.1) to demonstrate the daily amount does not exceed the daily limit

Control Correspondence (CC)

- Regulatory Support Branch has responded to:
- FY 2011 - 480 controls
- FY 2010 – 381 controls
- The current turnaround time is 60 days
- We no longer respond by e-mail to a CC. We will respond by telephone call

(CC) cont.

- Provide all the required information with request
- Determination is made similar to a filing review justification
- If an inactive ingredient is accepted by Regulatory Support, either via an ANDA submission or a Control Correspondence, it does not guarantee that there will not be issues during any one of the Divisional reviews

(CC) cont.

- Before submitting a Maximum Daily Dose CC you should cross-reference your request with your own approved ANDAs
- By doing this it may avoid such control and provide supporting justification for MDD in the future if needed
- We will not respond directly to CC from outside the US. Firms that are outside the US must submit their CC to OGD through their US Agent

(CC) cont.

- Maximum of 3 ingredients per CC (the more you submit the longer the response time could be).
- CC for multiple drugs for Q1/Q2 request should be submitted in separate request (maximum of 3 formulations per control)
- we will not pre-review formulations unless it is required to be Q1/Q2
  - **Reminder - CC reviews are a courtesy extended to industry**

PET Products

- As a result of section 121 of FDAMA, an NDA or ANDA must be submitted for any positron emission tomography (PET) drug prior to December 12, 2011.
- The Guidance for PET Drug Applications – Content and Format for NDAs and ANDAs was published August 2011

PET cont.

- This guidance is specific for:
  - Fludeoxyglucose F 18 Injection
  - Ammonia N 13 Injection
  - Sodium Fluoride F 18 Injection

PET cont.

- FDA expects to receive as many as 150 applications for PET products prior to December 12, 2011
- PET products will be prioritized upon receipt.
- These applications will reviewed by Team 41 with many of them consulted to OND. LCDR Dat Doan is the PM for team 41.

Summary

- The more information at the time of submission, the better
- Develop internal inactive ingredient database
- Do your homework!

Contact Information

- Martin Shimer, Branch Chief (240) 276-8675

Regulatory Management Officers:

- Kwadwo Awuah (240) 276-8678
- Peter Chen (240) 276-8977
- Rebekah Granger (240) 276-8724
- Shannon Hill (240) 276-8650
- Tim Jetton (240) 276-8967
- Craig Kiester (240) 276-8968

Contact Information cont.

Regulatory Management Officers:

- Iain Margand (240) 276-8676
- Saundra Middleton (240) 276-8973
- Ted Palat (240) 276-8982
- Felecia (Lisa) Tan (240) 276-8679
- Linh Vo (240) 276-8978
- Johnny Young (240) 276-8677

Support Staff:

- Jean Grimes (240) 276-8154
- Eda Howard (240)-276-8954
- Eddie Washington (240)-276-8957

Regulatory Support Branch